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Microreactors as the Key to the Chemistry Laboratory of the Future

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Abstract

The aim of synthetic chemists and the chemical industry is to perform chemical transformations in a highly efficient and environmentally benign manner. This involves atom economy and atom efficiency of the particular reactions on one hand; on the other hand it includes aspects of the reaction performance such as process safety, solvent and reagent consumption, and purification procedures. A well-engineered approach to elegantly overcome some of the aspects related to process performance is the use of continuous-flow microfluidic devices in chemical laboratories. This chapter highlights some application of these new tools in synthetic laboratories and how continuous-flow reactors may change the way chemists will perform their research in the future.

Introduction

Research chemists typically perform chemical transformations in traditional glass round bottomed flasks. Since the optimization of chemical transformations in batch reactors often consumes substantial amounts of starting materials, a lot of precious building blocks as well as effort and time are required in order to identify the ideal reaction conditions for a

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particular reaction. Having found the optimal conditions to achieve a certain reaction on a small scale, process scale-up often poses additional challenges and requires further adjustment of the reaction parameters. To overcome these hurdles in synthetic chemistry, microstructured continuous-flow reactors and chip-based microreactors are becoming increasingly popular [1].

Microstructured continuous-flow devices consist of a miniaturized channel system etched into or established on materials such as metals, silicon, glass, ceramics or polymers, which allows the chemical reaction to take place in a relatively narrow pore. These reaction systems have a high interfacial area per volume (only depending on the radius of the channel) and chemical reactions therefore profit from rapid heat and mass transfer. Due to the high heat and mass transfer rates, the reaction time, yield and selectivity are strongly influenced, often rendering processes to be more efficient and selective and thereby avoiding the generally required purification processes. Besides the facile control of the physical parameters, microreactors allow for low operational volumes to minimize reagent consumption, the integration of *on-line* detection modules and an excellent process safety profile in case highly exothermic reactions are undertaken, enhanced by the fact that only small amounts of hazardous/explosive intermediates may be formed at any given time. To obtain synthetically useful amounts of product, the reactors are simply run longer (''scale-out'' principle [1e]) or several reactors are placed in parallel (''numbering up''), assuring identical conditions for the analytical and preparative modes. Many different applications of microstructured devices in synthetic chemistry have been reported and reviewed; [2, 3] here some concepts and recent developments from our laboratory will be presented.

Microfluidic Reactor Types

Microreactors consist of a network of miniaturized channels often embedded in a flat surface, referred to as the ''chip'' [1a]. Since different chemical applications call for different types of reactors and materials, a variety of different possibilities have been explored. Additionally, the size of microfluidic devices strongly influences their application and the way in which reagents are introduced to the system [4]. The features of several selected microreactors are summarized in Figure 1 [5].

Most commonly, glass, stainless steel, silicon or polymers (e. g. poly(dimethylsiloxane), PDMS or poly(tetrafluoroethylene), PTFE) are used. Devices fabricated of PDMS are traditionally employed in biological and biochemical applications, [11] whereas stainless steel based microreactors are mostly applied in *meso*-scale production efforts [2b, 12]. Glass devices allow for the visual inspection of the reaction progress [13] or for application to photochemical reactions, [14] whereas silicon reactors offer excellent heat transfer rates due to the high thermal conductivity of silicon and therefore often are the reactors of choice due to their well established fabrication procedures [2 d, 3b–e, 15].

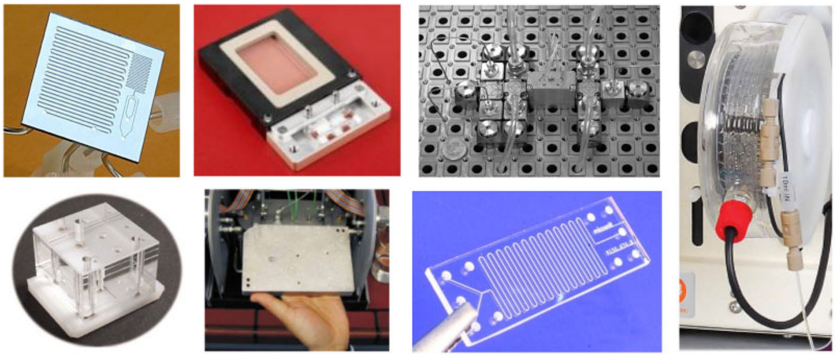


Figure 1. Selected microreactors; Top row from left to right: Silicon-based microreactor designed by Jensen [3b, 10]; Glass microreactor by Syrris® [6]; Stainless steel microreactor system by Ehrfeld Mikrotechnik® [7]. Bottom row from left to right: Glass microreactor by Haswell [1b, 1 l]; Stainless steel microreactor of the CYTOS® Lab system[8]; Glass microreactor by Micronit Microfluidics®[9]; Large picture right: Vapourtec® tube reactor [10].

The initial investigations of our group employed a stainless steel microreactor system designed by Ehrfeld Mikrotechnik [3a, 7] (see Figure 1). We further focused on the application of silicon-glass microreactors [3b-e, 15] as the glass layer would offer the possibility to visually inspect the reaction and the silicon portion would provide a rapid heat transfer. Further investigations were carried out in commercially available glass and PTFE tube microreactors [3f-h, 6], and other system are currently under evaluation or being developed.

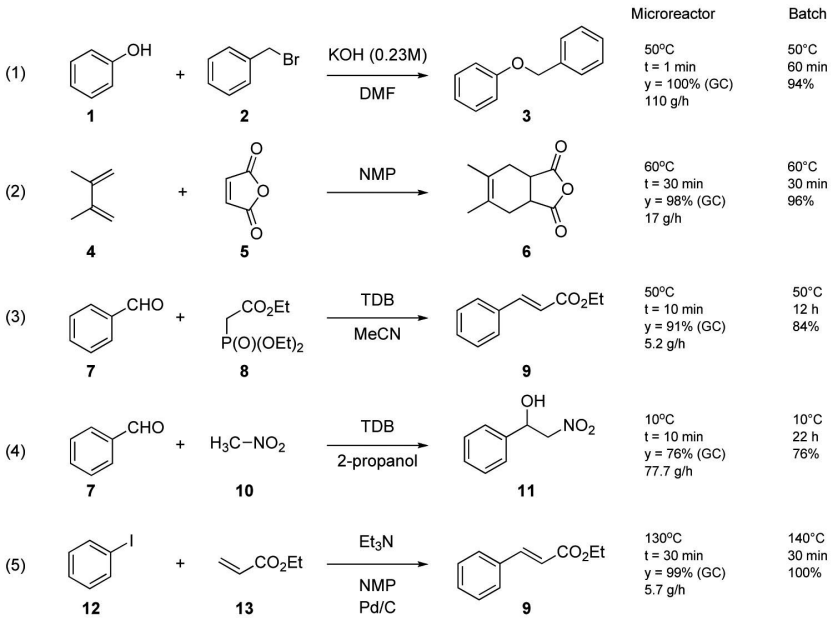
Synthesis in Microchemical Systems

Due to the small channel dimensions and the increased surface to volume ratio of microreactors, mass and heat transport are significantly more efficient than in the classic round-bottomed flask. The mixing of reagents by diffusion occurs very quickly, and heat exchange between the reaction medium and reaction vessel is highly efficient. As a result, the reaction conditions in a continuous-flow microchannel are homogenous, and can be controlled precisely. Therefore, highly exothermic and even explosive reactions can be readily harnessed in a microreactor. The careful control of reaction temperature and residence time has a beneficial effect on the outcome of a reaction with respect to yield, purity and selectivity. Below, selected examples from our laboratory are described to illustrate the potential application of microreactors to organic synthesis. The application of microreactors to small-scale medicinal and academic total synthesis is just beginning.

Chemical Reactions: Initial Investigations and Synthesis of Biopolymers

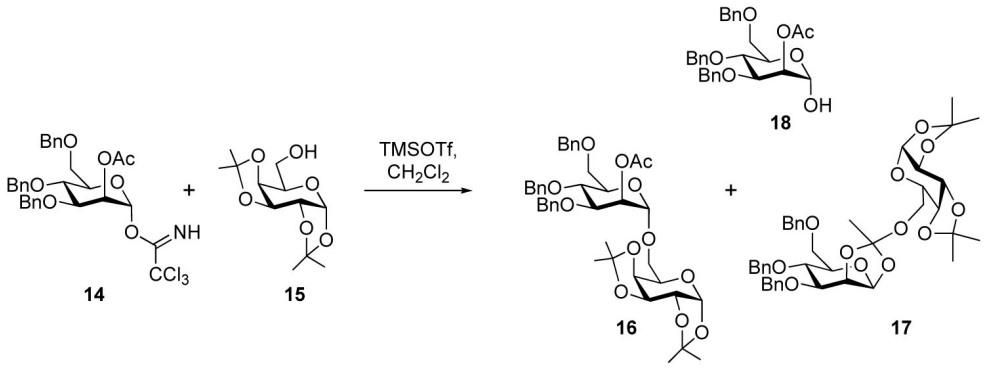
Liquid-phase reactions performed in micro structured devices benefit particularly from the efficient mass and heat transport characteristics of microreactors and the small amounts of reactants (e. g. hazardous reagent or intermediates, precious starting materials) being present in the system at any given time.

Our laboratory initially explored the relevance of microreactor technology in synthetic chemistry employing a stainless steel microreactor system (see Figure 1, Scheme 1) [3a]. The system was used to undertake various important synthetic transformations such as Williamson ether synthesis (eq. 1), Diels-Alder reactions (eq. 2), Horner-Wadsworth-Emmons reactions (eq. 3) and Henry reactions (eq. 4). Since a significant number of chemical transformations require solid catalysts to proceed in a reasonable reaction time and selectivity, investigations were undertaken to perform reactions of a heterogeneous nature in continuous-flow. A pre-packed reaction cartridge, loaded with an active catalyst on polymer beads, was placed in the continuous-flow system to allow palladium mediated cross-coupling reactions (Heck reaction, eq. 5) to take place [3a].



Scheme 1. Selected transformations carried out in a stainless steel microreactor system (y = yield) [3a].

The chemical synthesis of carbohydrate building blocks or small oligosaccharides remains a challenging task for synthetic chemists since a huge variety of components influence the outcome of a given glycosylation [3b, d]. The chemical outcome of such transformations depends strongly on the steric and electronic properties of the coupling partners, reagent concentrations, reaction temperature and reaction time. Furthermore, the building blocks used for oligosaccharide assembly often require multistep syntheses and are precious synthetic intermediates themselves. A silicon-glass microreactor, allowing for careful control of the reaction parameters, was employed to investigate glycosylations in continuous-flow (Scheme 2) [3b]. The small internal volume of 78 μL minimized reagent and building block consumption. The reaction progress of the coupling between protected mannoside **14** and galactoside **15** was monitored as a function of time and temperature (Fig. 2).



Scheme 2. Initial application of the silicon-glass microreactor to carbohydrate chemistry [3b].

It was revealed that at low temperatures (−80 °C to −70 °C) and short reaction times (< 1 min) the formation of orthoester **17** was favored, whereas higher temperatures (−40 °C) and longer reaction times (~ 4 min) led to formation of the desired α-linked product **16**. Using as little as 100 mg of starting materials, 40 different reaction conditions were scanned within one day [3b].

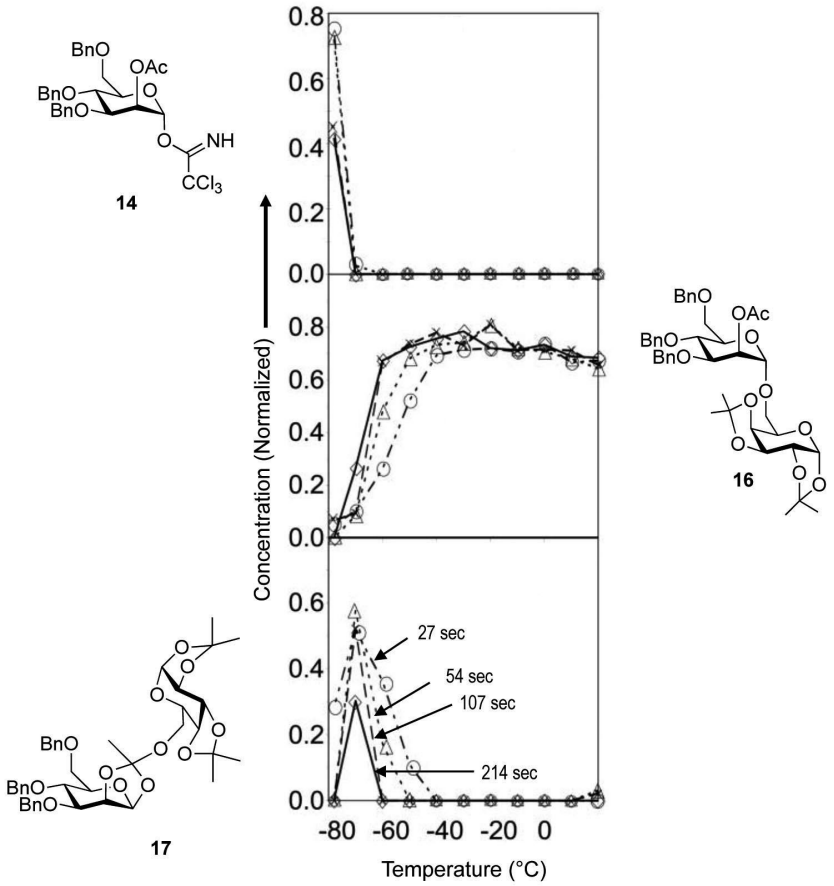
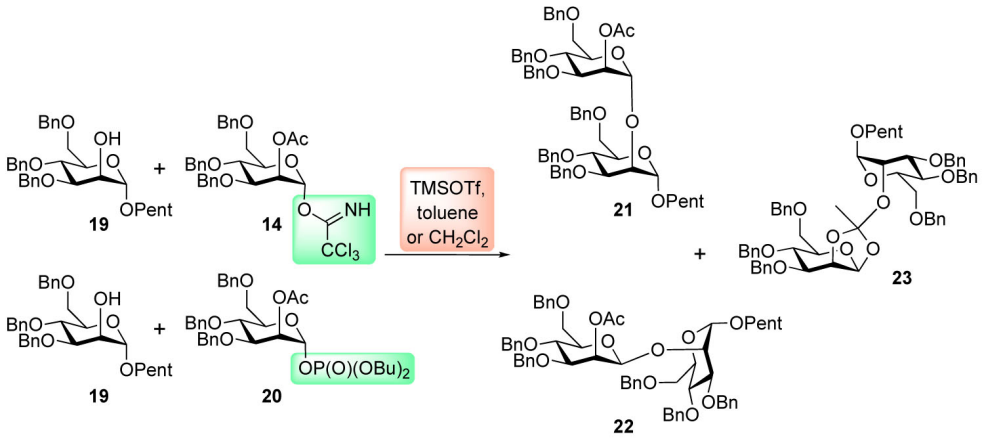
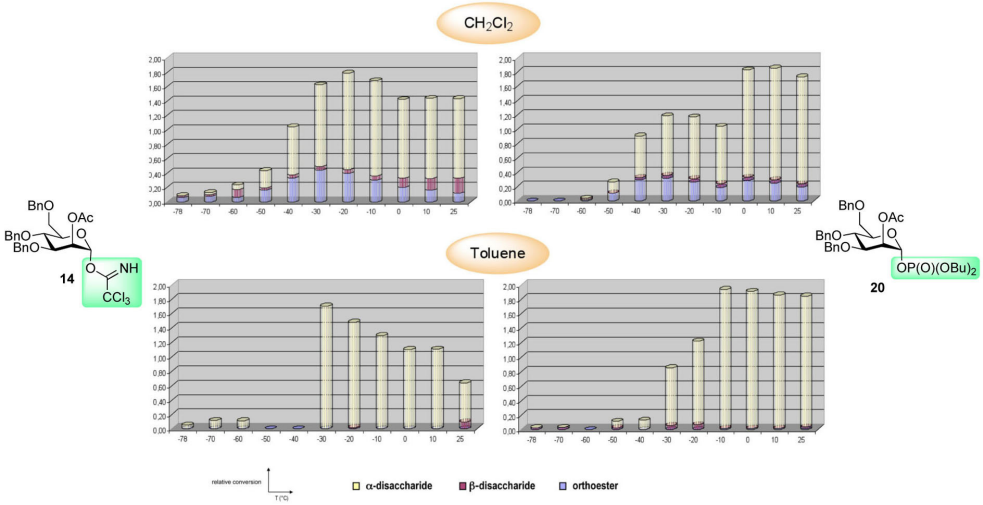


Figure 2. Starting material consumption and product formation of a glycosylation reaction [3b].

Having proven the applicability of the silicon-glass microreactor in carbohydrate chemistry, we were interested in investigating the influence of reaction temperature, reagent concentration, solvent and anomeric leaving group on the *selective* outcome of a given glycosylation. Therefore comparative studies employing mannosyl building blocks **14**, **19** and **20** respectively were undertaken to screen for the optimal reaction conditions varying reaction time, temperature, solvent and reagent concentration (Scheme 3) [3 d].



Scheme 3. Comparative studies of glycosylation reactions using varying glycosylating agents and solvent system [3 d].

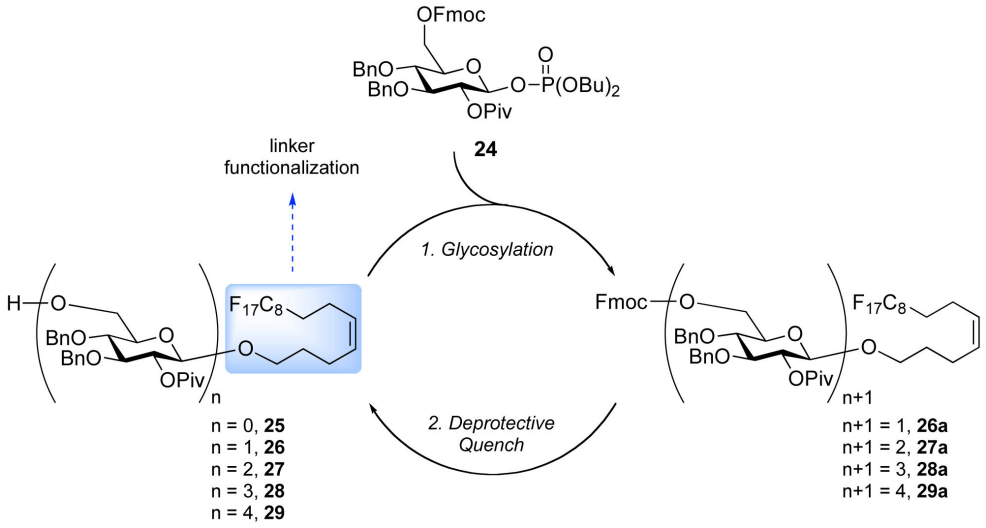


Building Block	Solvent	T (°C)	t (min)	Yield (%)	Batch Traditional
14	CH_2Cl_2	-20	4		
14	Toluene	-30	8	93%	Method A, -30°C, 60 min, 91-97%[15a]
20	CH_2Cl_2	+10	2		
20	Toluene	-10	2	81%	Method B, 0°C, 40 min, 74%[15b]

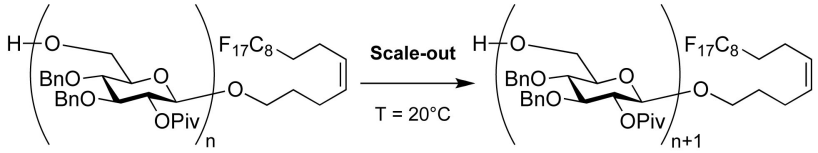
Figure 3. Product distribution at the optimal reaction conditions found by screening; Left side: Glycosylations employing reactant **14**; Right side: Glycosylations employing reactant **20**; **Table:** Scale-out of the optimized procedures [3 d].

It was discovered that glycosylations in toluene as the solvent proceeded more selectively than in dichloromethane (Fig. 3). While in dichloromethane even at optimized reaction conditions undesired β-disaccharide **22** and orthoester **23** are formed, α-disaccharide **21** is exclusively formed in toluene. Scale-up of the established synthetic procedures yielded the desired saccharide **21** in good to excellent yields (81% and 93% respectively) in short reaction times (2 min, 8 min) [3 d].

After having established the reaction conditions for single glycosylation reactions in silicon-glass microreactors, the synthesis of an oligosaccharide in continuous-flow was explored [3e]. Glycosylphosphate **24** was iteratively coupled to a growing carbohydrate chain on a perfluorinated support linker for facile purification by fluorous solid phase extraction (FSPE [17]) to deliver the desired oligosaccharides (Scheme 4). *In-situ* deprotection of the primary alcohol of each carbohydrate allowed for a reaction sequence of coupling and deprotection within reaction times of up to one minute per sequence to obtain the desired oligosaccharide in excellent yield (Scheme 5). The perfluorinated support linker of homotetrasaccharide **29** could, after successful assembly of the structure, be further functionalized to yield terminal olefins, aldehydes and trichloroacetimidates allowing for further synthetic transformations and attachment onto slides for biological investigations respectively (Scheme 6) [3e].



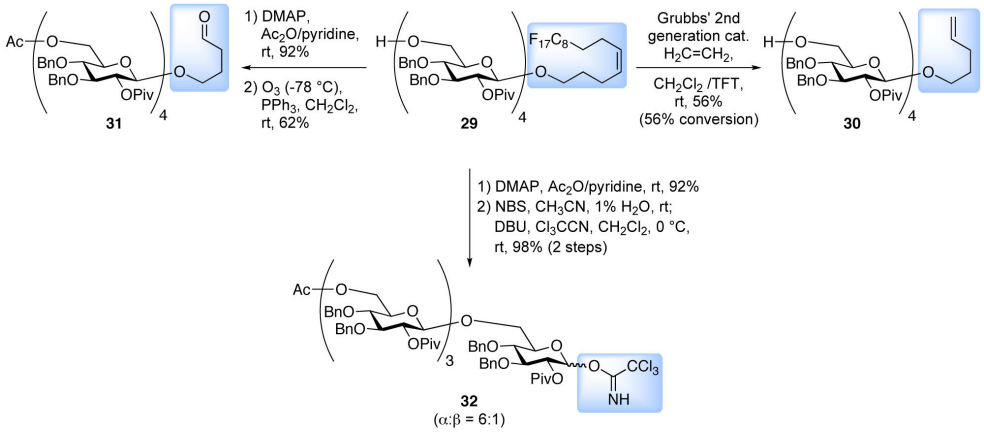
Scheme 4. Synthesis of the glucose based homotetramer **29** via iterative glycosylation [3 e].



nucleophile	scale (mmol)	solvent	time [s]	product	yield
n = 0, **25**	0.214	TFT	30	**26**	99%
n = 1, **26**	0.176	CH_2Cl_2	20	**27**	97%
n = 2, **27**	0.102	CH_2Cl_2	60	**28**	90%
n = 3, **28**	0.073	CH_2Cl_2	60	**29**	95%

TFT: Trifluorotoluene

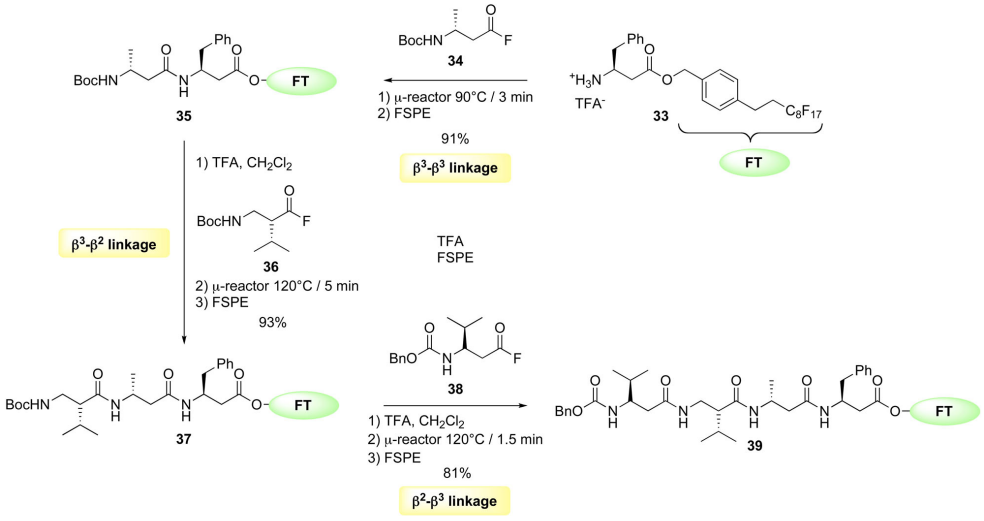
Scheme 5. Scale-out of the established coupling procedures [3e].



Scheme 6. Functionalization of the perfluorinated linker after successful assembly of the homotetramer **29** [3e].

β-Amino acid oligomers (β-peptides) present a unique class of peptides. In contrast to their natural α-amino acid derived counterparts, β-peptides show remarkable metabolic stability and are therefore of increasing interest for the pharmaceutical industry and the treatment of various diseases. Nevertheless, β-peptides require relatively few residues to form secondary structures like turns, helices or sheets [18], which usually leads to a lack of solubility in commonly employed solvents. Therefore, the synthesis of β-peptide structures is severely hampered [19]. Usually, high coupling temperatures are applied to circumvent precipitation of the peptides during the reaction, but the problem of low solubility remains unsolved for the required purification steps.

We investigated the application of a silicon-glass microfluidic reactor to the assembly of oligo-β-peptides (Scheme 7) [3c]. The microfluidic device thereby not only allowed for quick screening of reaction conditions and the controlled heating of the reaction mixture to unconventionally high temperatures, but also the procurement of synthetically useful amounts of peptides. The attachment of a perfluorinated linker again allowed for facile purification of the reaction mixtures by FSPE [17] to yield the desired oligopeptides **35**, **37** and **39** in excellent yields and short reaction times. Notably, the high reaction temperatures of up to 120 °C did not affect deprotection of the *tert*-butyloxycarbonyl (Boc) protected peptides, and highly reactive β^2-and β^3-homoaminoacid fluorides were employed for the β-peptide couplings. Furthermore, all possible β-peptide linkages were successfully installed, even the sterically most demanding β^3-β^2 linkage. Including global deprotection and cleavage from the perfluorinated linker the microreactor approach significantly increased the isolated overall yield of desired tetrapeptide **39** compared to solid phase or solution phase approaches (Scheme 7) [3c].



Entry	Approach	Yield
1	Microreactor	68%
2	Solution Phase	50%
3	Solid Support	55%

Scheme 7. Synthesis of a β-tetrapeptide in continuous-flow [3c].

Chemical Reactions: Evaluation of Microreactors for Hazardous Chemical Transformations and Scale-Up

More recently, we explored the applicability of microreactor technology for hazardous synthetic transformations that are unattractive, difficult or even impossible to be performed using batch procedures, especially on large scale. With the aim to speed up the transfer from development stage to production scales in chemical companies for synthetically useful transformations, we investigated reactions such as $AlMe_3$ mediated amide bond formations [3f], deoxyfluorinations using diethylaminosulfur trifluoride (DAST) [3 g], radical defunctionalisations and hydrosilylations in commercially available glass and tube microreactors (Fig. 4) [3 h, 6].

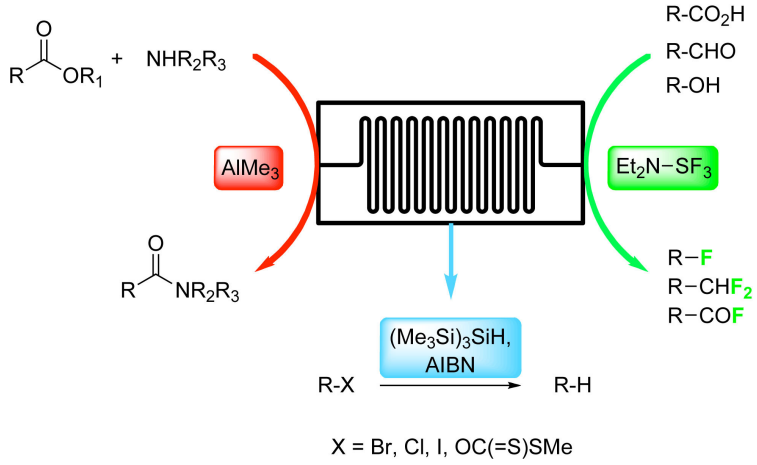
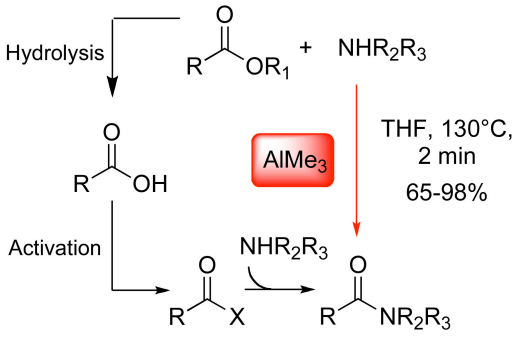


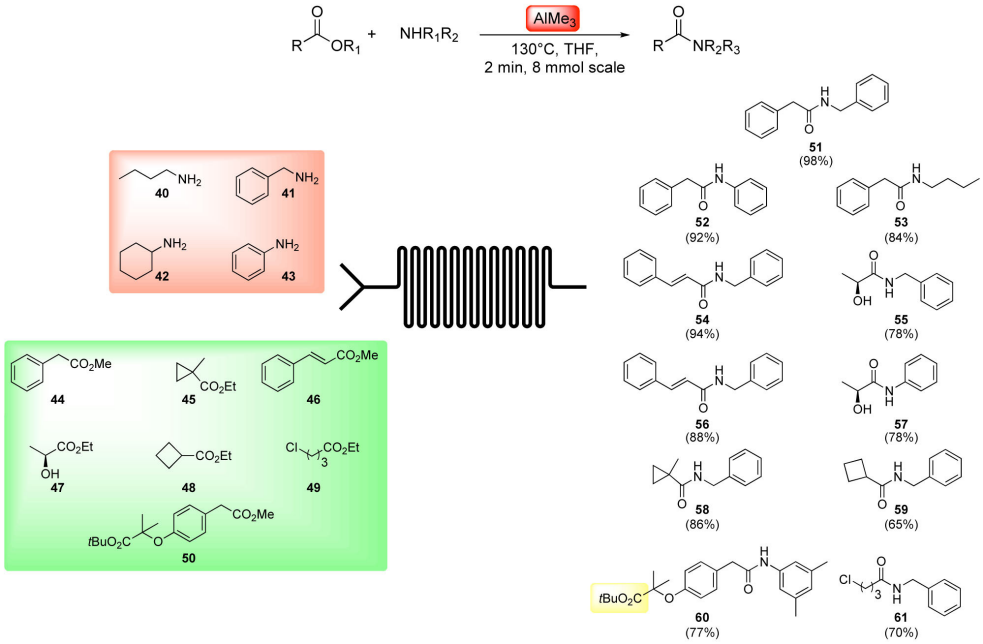
Figure 4. Microreactor based approaches toward hazardous reactions and scale-up chemistry [3f, g, h].

Amide bond formations are frequently used transformations in chemistry laboratories and generally require, starting from esters, a three step procedure including hydrolysis, activation and treatment with an amine to be synthesized (Scheme 8). Aluminium-mediated amide bond formations resembling direct Weinreb-amidation methods are, even though the reaction conditions render the transformation highly tolerant towards further functional groups in the molecule, less commonly applied due to the difficulties in safe handling of trimethylaluminium ($AlMe_3$). In addition, the aluminium-amide intermediates are unstable at elevated temperatures and are known to result in severe exotherms at room temperature. We investigated the applicability of microreactor technology for aluminium-mediated amide bond formation to develop a general protocol for the safe and rapid production of useful amounts of material (1 – 2 mol/day). A huge variety of primary and secondary amines as well as carboxylic acids derivatives were transformed into their corresponding amides in just two minutes reaction time (Scheme 9). Notably, installing a simple backpressure regulator

allowed for superheating of the solvents while still allowing for the reaction to proceed chemoselectively (amide **60**) and to tolerate functional groups such as carbon-carbon double bonds (54, 56), hydroxyl groups (**55**, **57**) or carbocycles (**58**, **59**).



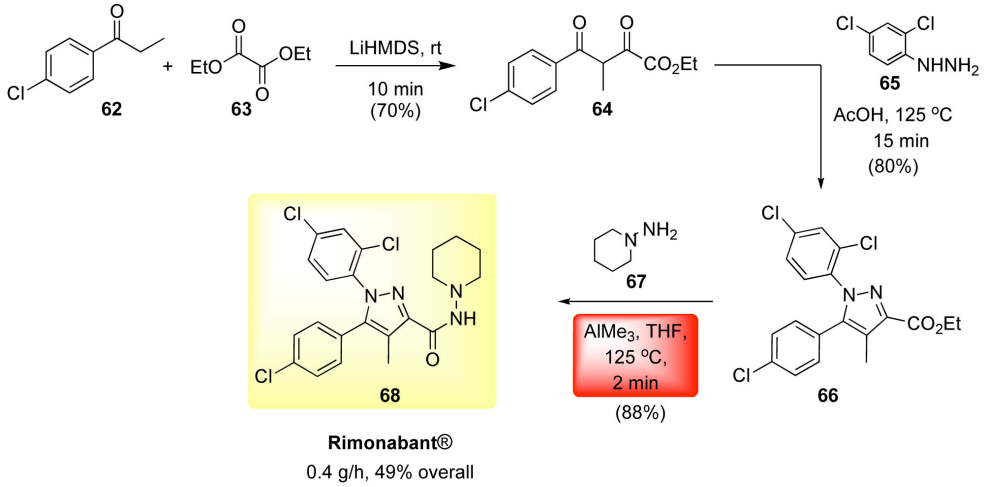
Scheme 8. General pathway for the formation of amides [3f].



Scheme 9. Selected examples for $AlMe_3$ mediated direct amide bond formation [3f].

The developed general synthetic protocol was further applied to the continuous synthesis of Rimonabant® (Scheme 10) [3f]. Rimonabant® is an anti-obesity drug by Sanofi-Aventis® that acts as a central cannabinoid receptor antagonist and is approved in Europe [20]. The entire synthesis was performed in continuous-flow, starting from aromatic ketone **62** and

diethyloxalate **63** to form diketone **64** in 70% over 10 min. Formation of pyrazole **66** was established in AcOH at 125 °C and a reaction time of 15 min. As the last synthetic transformation, the $AlMe_3$ mediated amide bond formation was performed to yield Rimonabant® 68 in an overall yield of 49% (Scheme 10) [3f].



Scheme 10. Synthesis of Rimonabant® **68** in continuous-flow with $AlMe_3$ mediated amide bond formation as the key step [3f].

Fluorinated biologically active organic compounds are of great interest in pharmaceutical industry due to their unique biochemical and physical properties. Besides the generation of fluorinated molecules by nucleophilic substitutions starting from halides and HF or KF [21], or electrophilic fluorinations of β-diketones via an enole pathway [22], deoxyfluorinations using deoxofluor or DAST are convenient reaction pathways due to the ready availability of unprotected hydroxyl functionalities in organic molecules [3 g, 23]. Nevertheless, the synthesis of fluorinated drug candidates, their precursors or organic molecules in general via deoxyfluorinations is severely hampered due to safety concerns. The most commonly used reagent DAST detonates at 90 °C, forms HF after contact with moisture or water which makes the use of special equipment necessary and is ideally avoided on large scale. We were interested in investigating DAST mediated deoxyfluorinations of alcohols, aldehydes, lactols and carboxylic acids in a continuous-flow PTFE tube reactor. Installation of a backpressure regulator allowed for superheating of THF close to the detonation point of DAST, and an *in-situ* quench with aqueous $NaHCO_3$ immediately destroyed remaining DAST or formed HF (Fig. 5) [3 g].

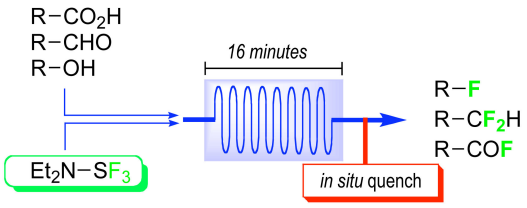
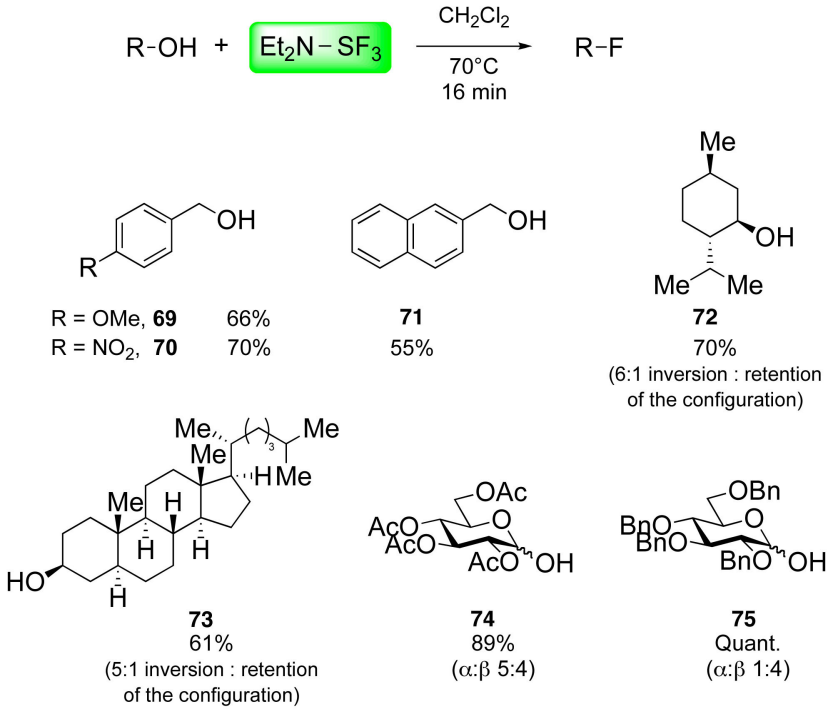


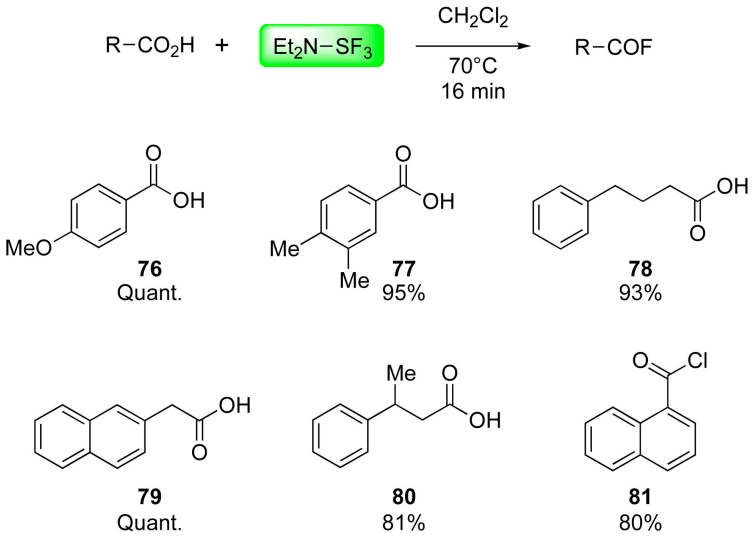
Figure 5. Overview of the DAST mediated deoxyfluorinations in continuous-flow [3 g].

Various primary and secondary alcohols underwent transformation into the corresponding fluorinated building block in high yields (Scheme 11). Consistent with the overall effort of our group to facilitate oligosaccharide assembly, electron rich and electron deficient glucosyl fluorides **74** and **75** were rapidly obtained in high yields from the corresponding lactols and did not require further purification before being used as glycosylating agents.



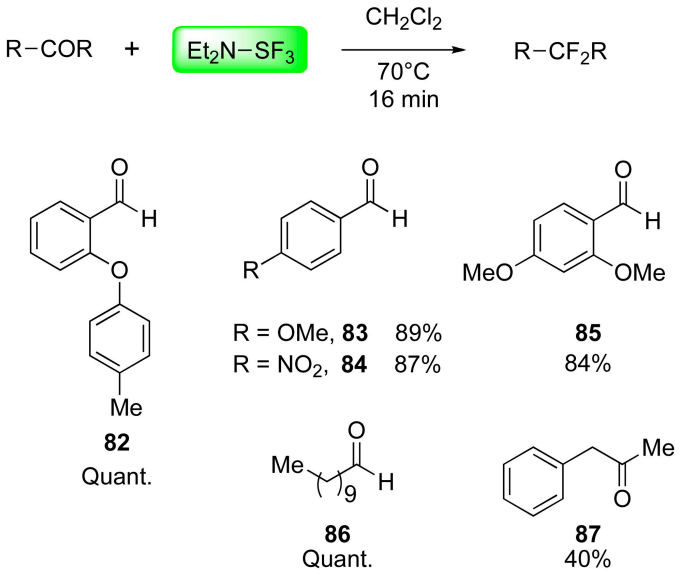
Scheme 11. Deoxyfluorinations of various alcohols and lactols [3 g].

In a further attempt to rapidly generate reactive intermediates, aromatic and aliphatic carboxylic acids were transformed into their corresponding acid fluorides (Scheme 12). Particularly impressive is the selective formation of the acid fluorides in case enolizable α-protons are present (**78**, **79**, **80**), no α-fluorination was observed. Furthermore, acid chloride **81** was selectively converted into the corresponding acid fluoride.



Scheme 12. Deoxyfluorinations of carboxylic acids and acid fluorides [3 g].

To generate difluoromethylene moieties, electron rich, electron deficient and sterically demanding aromatic aldehydes as well as aliphatic aldehydes underwent deoxyfluorination to yield the analogous fluorinated derivative in high yields (Scheme 13). Remarkably, ketone **87** as a sterically and electronically more challenging substrate, was transformed into the corresponding difluoromethylene derivative in 40% yield [3 g, 24].



Scheme 13. Synthesis of difluoromethylene moieties *via* DAST mediated deoxyfluorinations [3 g].

The latest investigations in our laboratories explored free radical mediated reactions such as dehalogenations, Barton-McCombie type deoxygenations and hydrosilylations in continuous-flow (Fig. 6) [3 h].

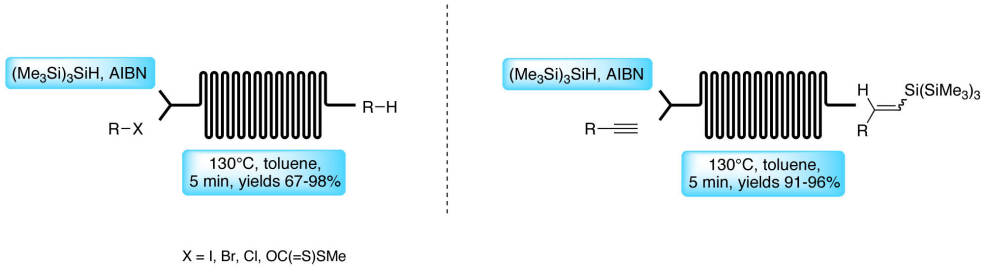
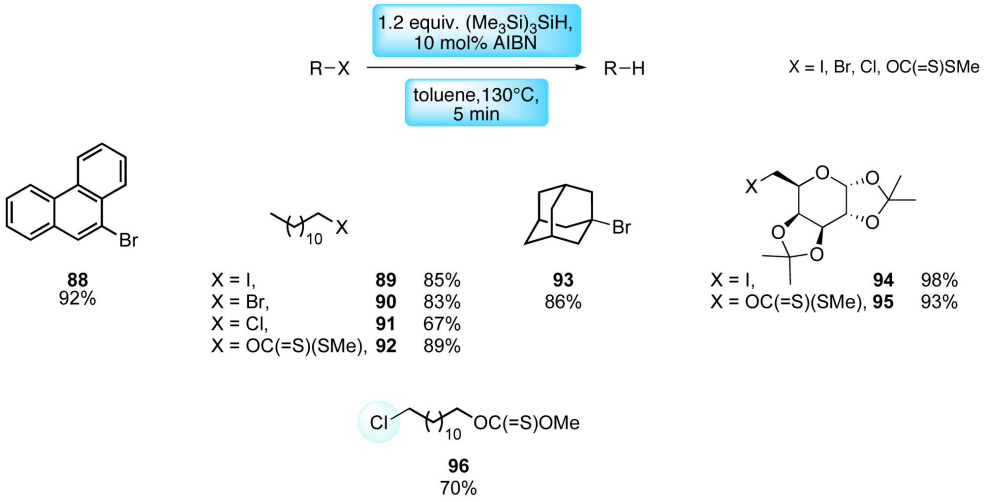


Figure 6. Free radical based transformations performed in glass microreactors [3 h].

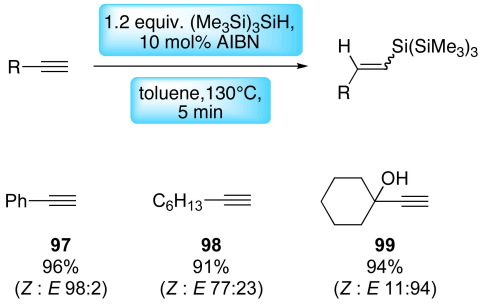
Deoxygenations and dehalogenations are important synthetic transformations since they are highly versatile reactions and tolerate a huge variety of further functional groups in the molecules. Unfortunately, the concentration of free radicals in the reaction mixture often influences the selective outcome of the reaction strongly. Careful control of the reaction temperature is required to circumvent thermal runaways. Investigating reactions in a continuous-flow glass microreactor using tris(trimethylsilyl)silane (TTMSS) as a non-toxic variant of the generally applied tin reagent Bu_3SnH resulted in high yielding dehalogenations and deoxygenations at a reaction temperature of 130 °C (superheated toluene,

established by a backpressure regulator) and a reaction time of five minutes (Scheme 14). Notably, taking advantage of the controlled reaction performance in the microreactor, the xanthate moiety of the difunctionalized dodecane **96** was removed chemoselectively [3 h].



Scheme 14. Radical mediated dehalogenations and deoxygenations in continuous-flow [3 h].

Hydrosilylations, the addition of Si-H bonds across unsaturated carbon-carbon bonds, are the most important synthetic transformation for the generation of organosilicon compounds. Especially tris(trimethylsilyl)silane TTMSS adds highly regioselectively to various alkynes via a free-radical chain mechanism to form vinyl silanes [25]. We envisaged that the rapid heat transfer in microreactors would effect the *E*/*Z* selectivity of the resulting silanes while significantly reducing the reaction time (Scheme 15).



Scheme 15. Hydrosilylations of alkynes performed in a glass microreactor [3 h].

Again applying reaction conditions of 130 °C in toluene and a reaction time of five minutes yielded the desired anti-Markovnikov products in excellent yields and good stereo-selectivities. The microreactor approach further furnished the hydrosilylation product of phenylacetylene **97** in greater yield (96% *vs.* 88%) and superior *Z*/*E* ratio (98:2 *vs.* 84:16) compared to traditional batch strategies [3 h, 25].

Conclusion

Many chemical transformations can be performed in a faster, safer and cleaner manner when performed in microfluidic devices. The down-scaling of reaction volumes in microreactors offers the more precise control of the reaction conditions (temperature, time, mixing) and the use of minimal amounts of precious compounds to rapidly screen a variety of conditions, generating a wealth of information on reaction kinetics and pathways. Additionally, microreactors present the opportunity to apply reaction conditions that are inaccessible using conventional laboratory equipment, such as super heated solvents, and safely performing reactions in explosive regimes. Even though numerous impressive examples on the application of microreactor technology in synthetic chemistry have been reported, some major drawbacks associated with this technique remain: the incompatibility of reactors with solid reagents that cannot be used for wall-coatings or be supported on linkers, the sensitivity to precipitations and the useful applicability mainly to fast reactions. Additionally, the efficient *on-line* analysis of reaction mixtures in a high throughput format represents an outstanding issue. The overall concept of highly efficient continuous-flow microreactor techniques requires further improvements before it will be applied as a standard tool in chemical laboratories.

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[4] Reagent introduction and feed can occur via electroosmotic flow, hydrodynamic pumping (HPLC pumps, syringe pumps) or capillary flow.

[5] A wide variety of other microreactors is available from other manufacturers and suppliers, *e.g.*: Institute for Microtechnology Mainz (IMM), Fraunhofer Alliance for Modular Microreaction Systems (FAMOS), the Little Things Factory (LTF) in Ilmenau, the New Jersey Centre for MicroChemical Systems (NJCMCS), the Micro-Chemical Process Technology Research Association (MCPT), or Sigma-Aldrich. The selection presented here is by no means exhaustive and only serves to indicate the diversity in systems developed to date.

[6] For further information visit the webpage: http://www.syrris.com/.

[7] For further information visit the webpage: http://www.ehrfeld.com.

[8] For further information visit the webpage: http://www.cpc-net.com/cytosls.shtml.

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